REMARKS

Applicant respectfully requests reconsideration of the present application in view of reasons which follow.

1. **Claims 20-24 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Johnson in view of Libman and the Manual of Clinical Microbiology, and further in view of Carr.**

This rejection is respectfully traversed. The Examiner has rejected the pending claims, stating that it would have been obvious to one of ordinary skill to have included the substrates of Carr in the methods of Johnson, Libman, and the Manual of Clinical Biology (MCB) to arrive at the present invention (Office Action mailed 6/15/01, p. 4).

The Applicants submit the attached Declaration of Chun-Ming Chen, Ph.D. Dr. Chen has utilized the MacConkey agar medium of Johnson, Libman, and the MCB and added a substrate of Carr (a 4-methyl-umbelliferyl phosphate substrate) in the MacConkey agar, as the Examiner alleged this medium (the "Johnson et al. medium") would meet the limitations of the present claims. Using this media, a comparison with an embodiment of the presently claimed media was conducted.

As Dr. Chen explains (¶¶ 10-12), the results show the resulting media failed to meet the limitations recited in the present claims. The present claims recite providing an assay device with a well containing a uropathogenic specific medium, which allows for the growth of the primary gram negative urinary pathogens and for substantially less growth of any other bacteria of a biological matrix. The claims recite other wells containing an antimicrobial susceptibility interpretation medium. Growth in the uropathogenic specific medium indicates the presence of urinary pathogens in the sample, and growth in the antimicrobial susceptibility interpretation medium indicates the organisms lack susceptibility to the antimicrobial agent in the medium. It is noted that the specification defines a "uropathogenic specific medium," as "a medium which allows only the growth

of the primary urinary gram negative pathogens and allows for substantially less growth of any other bacteria of a biological matrix." (specification, p. 12). And the "primary gram negative uropathogens" are defined as "the group of bacteria which cause at least 85-90% of the human and veterinary urinary tract infections." (p. 10 of the specification).

It is important to consider Dr. Chen's comments at ¶12 of the Declaration. Dr. Chen notes that 85-90% of the urinary tract infections are caused by gram negative bacteria. The remaining 10-15% are caused by gram positive bacteria. The media of the present invention focus on the detection of UTI organisms that cause the 85-90%. In order to achieve detection of "the group of bacteria which cause at least 85-90% of the human and veterinary urinary tract infections," (specification, p. 10, line 19) one must be able to detect all or virtually all the gram negative organisms known to cause urinary tract infections.

As evidenced from the data submitted in the Declaration, the medium of Johnson et al. is unable to detect "the group of bacteria that cause at least 85-90% of the human and veterinary urinary tract infections." (See Table I, p. 4 of the Declaration). Instead, the medium produced a very high number of false negatives. The medium also necessarily failed to perform the susceptibility testing recited in the claims, because it was unable to perform the initial detection of primary gram negative uropathogens (¶ 9).

Therefore, the present invention is not obvious over Johnson, Libman, and the MCB, in view of Carr, because the asserted combination does not teach or suggest all of the claimed limitations. The combination proposed by the Examiner fails to enable the person of ordinary skill to achieve the media recited in the present claims. Furthermore, no motivation exists to make the proposed combination, and even this inappropriate combination does not result in a useful product. Finally, there is no reasonable expectation of success in making the (inappropriate) combination of references and, in fact, the combination was not successful. All of these reasons are fully supported by the data provided by Dr. Chen.

In view of these data, it is apparent that Johnson, Libman, and the MCB in view of Carr do not teach or suggest the presently claimed invention. The present invention was the result of sustained inventive work to arrive at a medium that achieves the limitations recited in the present claims. Reconsideration and withdrawal of the rejection is respectfully requested.

2. **Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson, in view of Libman, the Manual of Clinical Microbiology, and Carr, as applied to claims 1-24, and further in view of Brocco.**

This rejection is respectfully traversed. Brocco fails to cure the deficiencies noted above. Brocco does not teach a medium specific for any organism. And the organisms assayed in Brocco must be pre-grown and added to the test medium as pure cultures, as is apparent from Example 1 of Brocco.

Reconsideration and withdrawal of the rejection is respectfully requested.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date November 15, 2001 By _____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Chen, Chun-Ming et al.

Title: METHOD AND APPARATUS FOR CONCURRENTLY DETECTING PATHOGENIC ORGANISMS AND ANTIMICROBIAL SUSCEPTIBILITY

Appl. No.: 08/942,369

Filing Date: October 2, 1997

Examiner: M. Moran

Art Unit: 1631

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date below.

Pridge McDougall
(Printed Name)

(Signature)

November 15, 2001
(Date of Deposit)

DECLARATION OF CHUN-MING CHEN, Ph.D.

1. I, Chun-Ming Chen, hold a Ph.D. in Food Science from Rutgers University, New Brunswick, New Jersey. I also hold a Master's degree from the University of Florida, Gainesville, Florida in Food Science. I have worked at the Food and Environmental Division at IDEXX Laboratories, Inc. as a microbiologist since 1993. I am the co-author of three patents in the area of microbiology, six peer-reviewed publications in the area of biochemistry and microbiology and another sixteen publicly-presented abstracts. A recent resume is attached to this Declaration.

2. I understand that the Examiner for this application has alleged that it would have been obvious to a person of ordinary skill in the art to arrive at the medium described in the pending claims of this application by utilizing the MacConkey agar medium taught by Johnson, Libman, and the Manual of Clinical Microbiology, and adding a detection substrate taught by Carr.

3. I designed the following experiment to determine if MacConkey agar combined with a detectable substrate of Carr is able to detect the presence of urinary pathogens in a biological fluid and determine the organisms' susceptibility to antimicrobial agents. I note that the present claims recite providing an assay device with a well containing a uropathogenic

specific medium, which allows for the growth of the primary gram negative urinary pathogens and for substantially less growth of any other bacteria of a biological matrix. Other wells are provided containing an antimicrobial susceptibility interpretation medium. Growth in the uropathogenic specific medium indicates the presence of urinary pathogens in the sample, and growth in the antimicrobial susceptibility interpretation medium indicates the organisms lack susceptibility to the antimicrobial agent in the medium.

4. Two sets of assays were constructed. The first set includes a well containing a representative example of the uropathogenic specific media (the "UTI medium") of the present invention, as disclosed on page 19 of the specification of this application. Two wells were also set up containing the UTI medium with fluoroquinolone and amoxicillin, respectively, to serve as the antimicrobial susceptibility interpretation medium described in the claims. Analysis of growth or lack of growth in these wells allows for the presence or absence of urinary pathogens directly from biological samples, with the simultaneous determination of antimicrobial susceptibility. A representative uropathogen specific medium of the present invention was constructed as follows: (quantities per liter); HEPES, free acid (6.864 grams), HEPES, sodium salt (5.292 gram), modified yeast nitrogen base (5.15 gram), yeast extract (0.5 gram), casein peptone (10 gram), potassium phosphate, monobasic (0.1 gram), bile salts #3 (0.75 gram), vancomycin (0.01 gram), amphotericin B (0.0022 gram), clindamycin-HCl (0.005 gram), and 4-Mu phosphate (0.05 gram). Ciprofloxacin, an analog of enrofloxacin, belonging to the class of fluoroquinolone antibiotics, was used in this study.

5. The second set of the assay used a MacConkey base medium with the addition of 4-Mu phosphate in an amount equivalent to that of the uropathogen specific medium of the present invention. Fluoroquinolone (2 mg/liter) and amoxicillin (8 mg/liter) were added to the MacConkey base medium, respectively, to determine whether antimicrobial susceptibility patterns could be determined for the detected gram-negative uropathogens directly from urine specimens. The MacConkey base medium used in this set contained the following ingredients (per liter): Bacto peptone (17 gram), protease peptone (3 gram), bile salts #3 (1.3 gram), sodium chloride (5 gram), neutral red (0.03 gram), crystal violet (0.001 gram), lactose (10 gram) and 4-Mu phosphate (0.005 gram).

6. A total of 97 different feline and canine urine specimens collected from animals suspected of having urinary tract infection (UTI), were tested with these two sets of media. A 60

ul aliquot of the urine specimen was added to 10 ml of sterile saline solution (0.85% NaCl solution). 100 ul of the diluted urine specimens was added to each media in the urinary tract infection device; the device was incubated for 24 hours.

7. For comparison, a traditional microbiological culture, bacterial identification, and antimicrobial susceptibility test were performed. A 1 ul portion of urine specimen was streaked onto a blood agar plate; the plate was then sub-cultured and subjected to biochemical identification to obtain the identity of the isolated culture. The antimicrobial susceptibility of the identified gram-negative urinary pathogen against the selected antibiotics (ciprofloxacin and amoxicillin) was determined by the standard Kirby-Bauer antimicrobial susceptibility assay.

8. Results of the experiment are summarized in Table 1 below. Among 97 urine specimens, 23 samples contained primary gram negative urinary pathogens as determined by traditional culture/bacterial identification technique. The results for the uropathogen specific medium of the claimed invention were exactly the same as for the traditional method, detecting all 23 of the 97 samples that contained primary gram negative urinary pathogens. Conversely, the MacConkey base medium (with the addition of 4-Mu phosphate) was able to detect only 14 samples that contained primary gram-negative urinary pathogens, as shown by the traditional method. It is also noted that among these 14 samples, 9 samples showed a weak and 3 showed a very weak fluorescent signal, causing some question as to whether these should even be scored as positive results. These results indicate that combining MacConkey medium with 4-Mu phosphate as a detection substrate failed to allow for the growth and accurate detection of the primary gram negative urinary pathogens, as recited in the claims. In addition, even more false negative results may frequently occur with this medium as evidenced by the weak fluorescent signal in 12 of the 14 positive samples found with the MacConkey base medium.

9. Because the MacConkey medium failed to accurately detect the gram negative uropathogens in the samples, it necessarily failed to perform accurate antimicrobial susceptibility testing, as shown in Table I below. This further illustrates that modifying the MacConkey medium by adding a substrate of Carr does not result in an accurate or useful test.

10. The results of this study clearly demonstrate that the MacConkey agar of Johnson, Libman, and the MCB with an added enzyme substrate of the Carr does not result in a medium described by the claims of the present application. The presently claimed medium allows for the growth of only the primary urinary gram negative pathogens (p. 12 of the specification), which

are defined at page 10 of the specification as the group of bacteria which cause at least 85-90% of the human and veterinary urinary tract infections. The media of the present claims also allow for the simultaneous determination of the susceptibility of the urinary pathogens to particular antimicrobial agents directly from biological samples. The medium of Johnson, Libman, and the MCB, combined with a substrate of Carr, failed to allow for the growth of primary gram negative urinary pathogens in a high number of cases.

Table I

	Gram (-)	Ciprofloxacin		Amoxicillin	
	Uropathogen	Resistant	Susceptible	Resistant	Susceptible
TMCSA[1]	23	0	23	13	10
Uropathogen Base[2]	23	1	22	13	10
MacConkey Base[3]	14[4]	1	13	8[5]	6

11. 85-90% of the urinary tract infections are caused by gram negative bacteria. The remaining 10-15% are caused by gram positive bacteria. The media of the present invention focus on the detection of UTI organisms that cause the 85-90%. In order to achieve detection of "85-90% of human and veterinary urinary tract infections," (specification, p. 10, line 19) one must be able to detect all or virtually all the gram negative organisms know to cause urinary tract infections. These results clearly show that MacConkey agar combined with 4-Mu phosphate is unable to detect "the group of bacteria that cause 85-90% of the human and veterinary urinary tract infections."

12. In view of the above results, it is apparent that combining MacConkey agar with the addition of a detectable substrate does not allow one to achieve the media recited in the claims of the present application. Nor do the Johnson, Libman, MCB, or Carr references provide any teaching or suggestion as to how to achieve the media recited in the claims. The media described in the present claims are the product of a sustained inventive effort.

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[1] TMCSA: Traditional microbiological culture and susceptibility assay.

[2] Uropathogen specific medium.

[3] MacConkey base medium with the addition of 4-Mu phosphate enzyme substrate.

[4] Among these 14 positive samples, 9 exhibited weak fluorescent signal and 3 showed very weak fluorescent signal.

[5] Among these 8 samples, 4 exhibited weak fluorescent signal and 4 showed very weak signal.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Chun-Ming Chen, Ph.D.

Date: Nov. 15, 2001

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Curriculum Vitae

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EDUCATION

Ph.D. Food Science (1988 – 1993) Rutgers University, New Brunswick, NJ
Dissertation: Purification and Characterization of 3,4-Dihydroxyxanthone Dioxygenase and Gentisate 1,2-Dioxygenase from *Arthrobacter sp.* Strain GFB100.
MS. Food Science (1985 – 1988) University of Florida, Gainesville, FL
Thesis: Microbiological Assessment and Controlling of Histamine Production in Yellowfin Tuna: Detection and Control of Histamine Producing Bacteria
BS Food Science and Nutrition (1977 – 1981) Fu-Jen Catholic University, Taiwan

EXPERIENCE

2001 to present
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1993 to 2001
Research Scientist — IDEXX Laboratories, Inc. Westbrook, ME
1993 (April – October)
Research Scientist — Environetics, Inc. Branford, CT (A Subsidiary of IDEXX Laboratories, Inc.)
1993 (February – March)
Postdoctoral Fellow — Rutgers University, New Brunswick, NJ

PUBLICATION

Patents

- Medium for Detecting Enterococci in a Sample. US Patent: 5,620,865
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- C.-M. Chen and K. Doherty. 1997. VRESELECT®: Rapid Detection of Vancomycin Resistant *Enterococci* Directly from Surveillance Specimens. C-006. The 97th Annual Meeting of the American Society for Microbiology.
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